Psychiatria Danubina, 2019; Vol. 31, Suppl. 2, pp S162-170 *Conference paper*

CLINICAL CHALLENGES IN PATIENTS WITH FIRST EPISODE PSYCHOSIS AND CANNABIS USE: MINI-REVIEW AND A CASE STUDY

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SUMMARY

The influence of cannabis use on the occurrence, clinical course and the treatment of the first psychotic episode (FEP) is well documented. However, the exact link is still not clearly established. The aim of this article is to review and report the noticed increase in the number of hospitalizations of young people with a clinical appearance of severe psychotic decompensation following cannabis consumption and to show the clinical challenges in treatment of the FEP. The case study describes the clinical course of a five selected patients with a diagnosis of the FEP and positive tetrahydrocannabinol (THC) urine test who were hospitalized in a similar pattern of events. They all have a history of cannabis consumption for at least 6 years in continuity and were presented with severe psychomotor agitation, disorganisation, confusion and aggression at admission. Although the chosen drug to treat all patients was atypical antipsychotic and benzodiazepines, the course of the disorder and the clinical response to therapy were noticeably different in each patient. The clinical presentation of FEP in cannabis users can be atypical and highly unpredictable from mild psychotic symptoms to severe substance intoxication delirium. In clinical practice clinicians treating new onset psychosis need to be watchful for cannabis and synthetic cannabinoids induced psychosis. Pharmacotherapeutic interventions include prompt and adequate use of the benzodiazepine, second-generation antipsychotic, and mood-stabilizers. Further research in the pharmacotherapy of cannabis-induced psychosis is required.

Key words: *cannabis - synthetic cannabinoids - psychosis - first episode psychosis - early-phase psychosis - schizophrenia - case study*

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INTRODUCTION

Cannabis and psychosis

There is a growing body of evidence that daily use of cannabis and the use of high-potency cannabis is associated with an increased odds of developing non affective psychotic disorders, especially for those with a pre-existing vulnerability and elevated familial risk for psychosis (Di Forti et al. 2019, Gage et al. 2016, Kendler et al. 2019, Mustonen et al. 2018). Yet, ascertaining causation is more challenging (Gage et al. 2017). About a third of all patients with first-episode psychosis (FEP) are also cannabis users (Meng et al. 2017, Myles et al. 2016). Overall, there is around 34% prevalence of clinically significant cannabis consumption in FEP, while the odds of continued cannabis use at the follow-up period declines by approximately 50% over time. (Myles et al. 2016). Many studies have found that the use of cannabis is connected with an earlier onset of psychotic illness and that this connection is based on several factors. A psychotic episode may occur almost three years earlier in the life of those who use cannabis when compared with nonusers (Myles et al. 2012) and there is an apparent linear connection between age of first cannabis use and age of the FEP, but also prodromal symptoms (Leeson et al. 2012). Starting cannabis at age 15 or younger may lead to earlier onset of psychosis, and increase the odds for the psychotic disorder but not independently of frequency or the potency of the cannabis used. (Di Forti et al. 2019, 2014, Mustonen et al. 2018). Some studies suggest that an earlier onset of psychosis may be due to a toxic effect of cannabis rather than a severe mental illness alone (Mustonen et al. 2018). Estimated time between first cannabis use and psychosis onset is around six years (Leeson et al. 2012). Furthermore, studies show that higher levels of cannabis use are associated with greater risk of psychosis, giving an odds ratio of 3.90 for the risk of a psychotic event among the heaviest cannabis users versus nonusers (Marconi et al. 2016). Additionally, there is also a firm argument that subjects who had been using high-potency cannabis (tetrahydrocannabinol (THC) ≥10%) on a daily basis had the earliest onset, approximately six years earlier than nonusers and it's the strongest independent predictors of whether any given individual would have a psychotic disorder or not (Di Forti et al. 2019, 2014).

Although the connection between THC and psychosis has been explored for decades, the relationship between novel synthetic cannabinoids (SCs) and psychosis is in its infancy. SCs products are "herbal" mixtures laced with various compounds that are sold around the

world under a variety of brand names to be smoked or consumed in other ways (Advisory Council on the Misuse of Drugs, 2014). In general, most biological effects of SCs mimic those of Δ9-THC; although the greater potency of SCs at cannabinoid-1 receptors produces stronger pharmacodynamics effects. The role of SCs in psychosis is complex, and whether prior SC use has a role in developing chronic psychotic disorders such as schizophrenia is still unclear (Deng et al. 2018).

Clinical manifestation

There is a lot of evidence that patients with psychosis who are regular cannabis users have more positive symptoms, more frequent relapses, and require more hospitalization (Hall & Degenhardt 2008, Patel et al. 2016). However, recent research presented no significant associations between continuation and cessation of cannabis use and positive and negative symptoms over the 2-year follow-up, while the depressive symptoms were significantly higher in patients who continued using cannabis (Hadden et al. 2018). When presented with a patient with psychotic symptoms and history of cannabis use, we may ask ourselves a question – "Is there a clear difference between clinical manifestation of a primary psychotic disorder with concurrent substance abuse (PPD+SA) and a substance-induced psychotic disorder (SIPD)?". Distinguishing these entities can be diagnostically challenging. A recent systematic review did not reveal many differences in the psychopathology. However, the findings indicate that patients with SIPD had both fewer positive and negative symptoms, but more depression and anxiety than patients with PPD+SA. Logically, patients with SIPD had a weaker family history of psychotic disorder but also a higher degree of insight (Wilson et al. 2017) and faired worse regarding occupational outcomes (O'Connell et al. 2018). Hence, O'Connell and colleagues found that 35.7% of those with SIPD had a change of diagnosis to a schizophrenia spectrum or bipolar disorder after a median of 84 weeks (O'Connell et al. 2018). But from a psychopathological point of view, „cannabis psychosis" may not be qualitatively any different than any other type of psychosis (Baldacchino et al. 2012, O'Connell et al. 2018, Thompson et al. 2016). A recent prospective cohort study came up with the results showing higher excitement symptoms at baseline in patients who used cannabis before FEP, as well as a better response for excitement and positive symptoms (Meng et al. 2017).

Excitement symptoms are often presented in the form of agitation which follows the fact that psychiatric patients are generally considered as potentially dangerous and aggressive, but despite the overall opinion, there isn't such a great connection between mental illness and violence (Fazel & Grann 2006). Since substance use has a clear relationship with violent behaviour in healthy individuals as well as in mentally ill, there is no wonder combining these two factors will contribute to the risk of agitation and aggression. However, the link between cannabis use and violent behaviour in FEP is unclear (Moulin et al. 2018). Although some research and reviews indicate that psychiatric patients who use cannabis show a higher risk of aggressive and violent behaviour (Carabellese et al. 2013, Dellazizzo et al. 2019, Dugré et al. 2017, Moulin et al. 2018).

Furthermore, a clinical presentation of SCs use is highly unpredictable (Kronstrand et al. 2013, Deng et al. 2018, Kolla & Mishra 2018). A recent observational study of a relatively large cohort of 594 SC users found that they were more severely psychotic than cannabis users. In particular, the SC users were more often diagnosed with psychotic disorders, were treated with higher doses of antipsychotic medications, and required longer hospitalizations (Bassir Nia et al. 2016). Characteristic symptoms of SC not seen in cannabis intoxication include enhanced aggression and agitation, seizures, hypertension, emesis, hypokalemia, and kidney injury (Deng et al. 2018, Gray et al. 2016, Kolla & Mishra 2018).

Cannabis and medication

Both medication non-adherence and co-morbid cannabis abuse are associated with poor clinical outcome in FEP, more frequent hospitalizations, increased rate of compulsory hospital admission and a greater number of days spent in hospital (Patel et al. 2016). The potential reason for such outcomes was a possible failure of antipsychotic treatment, indicated by the number of unique antipsychotics prescribed up to the 5 years follow up (Patel et al. 2016). This could mean that patients were either resistant to the given antipsychotic or poorly adherent to the treatment or that there were overwhelming side effects. Some patients could have had reduced dopamine synthesis capacity, which could reduce response to the antidopaminergic effect of antipsychotics (Bloomfield et al. 2014. Howes & Kapur 2014). Another possible reason for treatment failure could be the pharmacokinetic interactions between cannabis and other medications. For example, the main psychoactive part of cannabis, tetrahydrocannabinol (THC) and cannabidiol (CBD) are both metabolized by cytochrome P450 enzymes CYP3A4 and CYP2C9. Consequently, the CYP3A4 inhibitors may slightly increase THC levels, while CYP3A4 inducers slightly decrease THC and CBD levels (Stout & Cimino 2014). THC is a CYP1A2 inducer, and it can theoretically decrease serum concentrations of some psychiatric drugs such as clozapine, duloxetine, olanzapine, haloperidol, and chlorpromazine. Although there is extensive evidence about the effects of antipsychotic medications in FEP general, the efficacy and safety of antipsychotics on psychotic symptoms in patients with comorbid cannabis use is not clear, as such patients are usually excluded from clinical trials.

Intrigued by all the literature findings and questions raised by everyday clinical practice, we decided to assess the practical issues of cannabis use in patients with FEP from both psychopathological and psychopharmacological point of view.

SUBJECTS AND METHODS

This study describes a case series of five FEP patients with positive THC urine test who were presented with severe agitation at admission, besides other psychotic symptoms, and was pharmacologically challenging to treat. They were all treated at the Centre for Integrative Psychiatry in Psychiatric Hospital "Sveti Ivan", Croatia. The data was collected from electronic documentation for each patient individually and based medical history information, as well as psychiatric interviews, conducted multiple times during the hospitalization, laboratory blood and urine tests, nurse documentation, psychological and neurological examinations.

RESULTS

Clinical cases

Case 1#

A 26-year-old man, with no history of psychiatric illness, is brought into hospital's emergency room (ER) by an ambulance and police, and his brother after he punched his mentor because he thought he was working on a machine that would destroy the world. On admission, he is present with extreme agitation, confusion, and disorganization. He is leaping, running, shouting, laughing, crying, and insulting the policemen and the medical stuff, vulgar, noncompliant and unaware of his condition. After initial clinical assessment, he remains uncooperative and disruptive, subsequently, he was physically restrained and given intramuscular (IM) haloperidol 10 mg, and intravenous (IV) diazepam 20 mg was administered, to prevent harm to himself or others. Next day after admission, the psychotic production fades, mood, psychosis, and aggression improve, and the patient is calmer and compliant. He had tested positive for THC, other laboratory studies completed during he's hospitalization are unremarkable.

He grew up in a dysfunctional family, and he was often subjected to mockery and mistreatment by peers. At the age of 15, he began smoking marijuana intensively, which continued to date. After the breakup of only emotional relationship, two years ago, he became more consumed by cannabis, and he experimented with psilocybin mushrooms. A week before hospitalization, the patient describes that something "clicked in him," and he started believing in God, reading hidden messages from random conversations, realizing that the universe works at 430Hz.

His inpatient medication regimen with risperidone a 2mg/day, lorazepam a 3 mg/day and sodium valproate 600 mg/day was effective for his psychotic symptoms, but within few days, he developed bilateral tremors, and rigidity on upper limbs, which were manifestations of extrapyramidal symptoms (EPS). A probable diagnosis of risperidone-induced EPS was, made and the drug was withdrawn. He was started on 10 mg aripiprazole for his psychotic symptoms and was discharged after 13 days on LAI aripiprazole a 400 mg monthly in complete resolution of symptoms.

Case 2#

A 27-year-old man, with no history of psychiatric illness, was brought into hospital's ER by an ambulance and accompanied by three policemen, after being found wandering in a psychotic state on a highway near the state border. On admission, he is present with agitation, disruptive, and unpredictable behavior, irritable, shouting, and threatening staff members. He developed increasing paranoid concerns that his family has turned against him and that an assassin was sent to kill him. He was frightened and went to the state border to escape to another country where his suspicions about the conspiracy would be heard. He has been treated with risperidone a 2 mg/day and lorazepam a 3 mg/day.

He grew up in a dysfunctional family. At the age of 16, he begins to consume cannabis. Gradually, the condition stabilizes for 3 days, but two days after the initial stabilization, the patient becomes restless, confused and disorganized, extremely demanding, presents a variety of delusional ideas, and a paranoid concerns. Diazepam IV 20 mg was administered, and the dose of risperidone was increased to 4 mg/day due to poor symptom control. Following the modification of therapy, the patient is quickly calmed down. After 15 days of treatment in the acute ward, he is eventually transferred to the psychotherapeutic department. After a total of 50 days of hospitalization, the patient is discharged in a compensated mental state on paliperidone palmitate 100 mg monthly, diazepam 5 mg/day and zolpidem 10 mg/day.

Case 3#

A 21-year-old female, with no history of psychiatric illness, is brought into hospital's ER accompanied by emergency medical services after her boyfriend called the police because she manically ran around the apartment, threatened with suicide, and locked herself in the toilet. Upon arrival in the hospital, she starts to resist, paranoid interpretation of reality was present, she was extremely aggressive, unmanageable. She took medications after long persuasion. To address her symptoms, she received olanzapine 5mg/day, and diazepam IV 20 mg was administered.

She was born in a dysfunctional family where there was often physical violence, and she was often found fleeing from home. From the age of 15, she is regularly using cannabis. Three months before being admitted,

she began to behave bizarrely. According to the sister, she often smoked weed, had dramatic mood oscillations, religious delusions, and was physically aggressive.

Three days after admission, she is calm and cooperative, agrees to therapy, states that she believes that her medication helps her, and realizes she needs treatment. On the fifth day, the psychotic symptoms exacerbate, she again refuses therapy, is paranoid and aggressive towards the medical staff. She received diazepam IV 20 mg and starts risperidone 2 mg/day, and oral clonazepam 0.5 mg was also added to relieve anxiety and sedate the patient. Despite the modification of therapy, the patient's psychological state was oscillating day by day. Clonazepam is switched to quetiapine, 25 to 50 mg as needed, to address ongoing mood oscillation and insomnia and to reduce the risk of dependency on clonazepam. All laboratory studies completed during she's hospitalization are unremarkable. Urine drug screen was positive for THC. She does not undergo any head imaging. During hospitalization, quetiapine dose was increased to 200 mg/day. Over the next few days, her mood, psychosis, and aggression improve. The tenth day of treatment, her condition stabilized After 16 days of hospitalization she is calm and cooperative, mood, psychosis, and aggression improve. She denies suicidal or homicidal ideation and is deemed safe for discharge. She was discharged on LAI risperidone 25 mg bimonthly and quetiapine 200 mg/day.

Case 4 #

A 24-year-old man was brought to the ER with emergency medical services. He was disorganized, refuses contact, prays, and wants to talk only with the Pope. Upon arrival, he becomes physically aggressive towards the staff, and had to be restrained. He refused therapy, and IM haloperidol 10 mg and IM diazepam 10mg are applied after which he calmed down.

In childhood, he had problems with a stutter and involuntary body movements, which is why peers teased him, and often physically abused him. He started to consume cannabis when he was 16-year-old. His family and friends describe him as passive, withdrawn, obedient. The day before the reception to the hospital, the patient began to behave differently; he was in an elevated mood, quick and extensive in contact, agitated, which was unusual for him. His father tried to get him to the ER, but he ran away from the car. The second day after admission, he was still agitated, aggressive, and uncooperative, he displayed significant disorganization and thought blocking. He received IM olanzapine 10 mg but in the evening he became aggressive, hostile and disorganized again. His agitation resolved following acute administration of IV diazepam 20 mg, and antipsychotic treatment was change to risperidone 2 mg/day. All laboratory studies completed during he's hospitalization are unremarkable. A urine drug screen was positive for THC. His mental state oscillated, at times he was uncooperative, and his psychotic symptoms remained fluctuant and have sleep disturbances. He received a combination of paliperidone palmitate 100 mg and clozapine 250 mg with augmentation from sodium valproate 600 mg. Gradually his sleep is regulated, the psychotic symptoms are paling; he is critical to THC consumption, and negates craving. After 18 days of treatment in the acute ward, he had been transferred to the psychotherapeutic department. After two weeks of psychotherapy treatment the patient and his family insist on discharged. He was released in an uncompleted remission with a recommendation to continue with the following medication: paliperidone palmitate 100 mg, clozapine 250 mg, sodium valproate 600 mg, and lorazepam a 3 mg.

Case 5 #

A 24-year-old man, with no history of psychiatric illness, was brought into the hospital's ER by an ambulance and accompanied by ten policemen for inadequate and bizarre behavior in public. On admission, he is present with religious delusions, calling himself an omnipotent god. He is disorganized, restless, verbally, and physically aggressive toward staff members. He received IV diazepam 20 mg and risperidone 2 mg/day, which helps to alleviate his disruptive behaviors.

He has always had problems adapting to a new environment and has a feeling that he does not belong anywhere. He begins with the consumption of various drugs at the age of 17 of which only cannabis is consumed regularly. Half a year before arriving at our hospital, he feels excess energy and frequent mood changes.

The next day, after he sleeps through the night, he does not remember the events that preceded his admittance. He was calm, cooperative, accepts medications and treatment. Over time and with adequate treatment (risperidone 4 mg/day and clonazepam 0.5 to 1 mg as needed) resulted in gradual normalization of vital signs along with psychotic symptoms and behavioral control such that he returned to his baseline mental status and was discharged on hospital day 12.

Case review

In this case study, the status of five selected patients is monitored, four male and one female, aged between 21 and 26 admitted at the hospital under the clinical appearance of the FEP and a positive THC urine test. They are hospitalized after a similar pattern of events, following police intervention and emergency medical assistance and arrive disorganized, confused and hostile, with disruptive and unpredictable behavior. Upon arrival, initial assessment and routine laboratory processing were performed. After patients, acute symptoms were stabilized, a neurological, and psychological examination was performed. The patients` laboratory findings were within normal limits, and in all cases, acute neurological events were excluded. Interestingly, all patients come from dysfunctional primary families with negative psychiatric history with experience of early childhood

trauma. They all have a history of cannabis consumption for at least 6 years in continuity together with occasional experimentation with other psychoactive substances. On average, the onset of cannabis use is at the age of 16. According to psychological testing and responses in the Applied Personality Questionnaire (PAI), it is common for everyone to emphasize impulsiveness, an inclination to beware and risk behavior, aggressive coping with problems, weak control of hostile reaction in relationships, and weakened tolerance on frustration in the personality domain. Although the chosen drug to treat all patients was an atypical antipsychotic course of the disease and the clinical response to therapy was noticeably different in each patient. The duration of hospitalizations was from 13 to 50 days. Two out of five patients continued treatment at the psychotherapeutic department after treatment in the acute department. Two out of five patients experienced a relapse within a year after being released from our hospital, notably both of them did not continue to take antipsychotic medications and continued with cannabis use.

The clinical presentation differs significantly among patients. In two patients, it was noted that within 12 hours of application of the drugs, the psychotic substrate fades and rapid recovery occurs. Meanwhile, in the other three patient's mental state highly oscillated for days followed by gradual improvement of the mental state. As mentioned, the drug of choice was atypical antipsychotic, and depending on the clinical appearance, a mood stabilizer, anxiolytic, and other atypical antipsychotics at low doses. The response to therapy is noticeably different in each patient, and the clinical appearance of the FEP is atypical, although we notice the significant agitation improvement upon administration of a high dose of IV benzodiazepines.

DISCUSSION

Based on our observation and experience, the clinical manifestation of FEP in patients who are also cannabis users can be unpredictable. As seen from given examples, symptoms may vary from well-known psychotic signs such as delusions, hallucinations, or negative symptoms to the severe psychomotor agitation, irritability, or aggression. Some studies found that duration of untreated psychosis (DUP) is shorter among substance-induced psychotic disorders (SIPD) than in primary psychotic disorders with concurrent substance abuse (PPD+SA) (Wilson et al. 2017). With all the given information, we might ask ourselves - does the cannabis use affects the incidence rates of psychotic disorders? One of the recent studies found a correlation between the incidence rates for psychotic disorder and the prevalence of daily cannabis use in controls. The incidence rates were highest in areas where an everyday use and use of high-potency cannabis (THC ≥10%) was more prevalent (Di Forti et al. 2019). In our study, all the presented patients had no previous medical record of psychiatric illness, as well as no family history of schizophrenia or other psychotic disorders. All this information is in accordance with the observations from the relevant literature, which indicates that cannabis use may induce acute psychotic experiences and affect the severity of psychotic symptoms. There have been reports of a 2-fold increase in the risk to develop a psychotic disorder in average cannabis users compared to nonusers as well as approximately a 4-fold increase in risk for the heaviest users (Henquet et al. 2005, Marconi et al. 2016, Moore et al. 2007, Semple et al. 2005) According to one study, SIPD patients experienced significantly more severe symptoms of mania and disturbed behaviour compared to those with PPD + SA, but these findings were only significant on admission to hospital and symptoms diminished rapidly (Dawe et al. 2011). Our patients also followed this pattern and were presented with severe symptoms of agitation, aggressive behaviour, hostility, delusions, visual and auditory hallucinations, and persecution ideas when admitted to the hospital. However, the response to the applied therapy was variable, from rapid improvement within 12 hours, through the oscillation of the symptoms daily to the gradual stabilization of the mental state in the following ten days. This could lead us to a few very different paths. If we observe described patients through the loop of cannabis-induced psychotic disorder, one of the possible explanations of such a dramatic clinical appearance is the fact that nowadays cannabis has higher potency and the level of THC (tetrahydrocannabinol) in illicit cannabis samples has grown from around 4% during 1995 to almost 12% in 2014, while the level of CBD (cannabidiol) fell. In other words, cannabis is stronger now than it was twenty years ago (ElSohly et al., 2016). Surely we didn't have the opportunity to analyse the cannabis samples and to examine the potency of it, but high potency cannabis could be one of the reasons for severe agitation in presented patients. The other reason for more aggressive symptoms in patients with FEP is a relatively high percentage of use of novel psychoactive substances (NPS) among people between ages 18 and 50 in our country. One of the epidemiological studies revealed that 19.1% of people in Croatia who goes to the night clubs had tried some of the NPS at least once in a lifetime (Glavak Tkalić et al. 2018). Psychopathological symptoms associated with NPS, in particular with SC use in comparison with natural cannabis include severe sleep problems, hypomanic symptoms, somatization, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism (Mensen et al. 2019). Since the possibilities to detect synthetic cannabinoids in organic samples such as urine are very limited, we cannot be sure if some of the patients could use some of the unknown and undetected NPS.

Table 1.

Brief Psychotic Episode*	Delirium*	Symptoms Of Described Patients
Presence of one (or more) of the following symptoms: delusions, hallucinations, disorganized speech (e.g., frequent derailment or incoherence), grossly disorganized or catatonic behavior.	A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).	Extreme agitation, hostility, disorientation, disorganization, attention disorders, delusions, and hallucinations, lost the ability to test reality, verbal and physical aggression were present.
Duration of an episode of the disturbance is at least 1 day but less than 1 month, with eventual full return to premorbid level of functioning.	The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.	The course of the disease was different in each patient. In some, the disturbance developed in a short period of time, and in others for a longer period. Furthermore, an episode of the disturbance had a different duration in each patient; from one day to a week with fluctuation in the severity of symptoms during the course of that week.
The disturbance is not better explained by major depressive or bipolar disorder with psychotic features or another psychotic disorder such as schizophrenia or catatonia, and is not attributable to the physiological effects of a substance (e.g., a drug of abuse,a medication) or another medical condition.	An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).	According to medical history data, psychological and neurological examinations in all patients were not registered any other neurological or mental illness
	These disturbances are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.	The patients` laboratory findings were within normal limits, and in all cases, acute neurological events were excluded.
	There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.	All of the patients had positive tetrahydrocannabinol (THC) urine test.

* Diagnostic criteria based on a DSM-V

Another interesting question could be observed from a diagnostic point of view, and a clinician could find himself in doubt when presented with a patient with obvious psychotic symptoms. But when we carefully scroll through diagnostic criteria, psychotic symptoms may occur in many different mental states, beside psychotic disorders on its own. For example, psychotic symptoms can occur in a substance intoxication or substance withdrawal delirium. According to the fifth edition of Diagnostic and statistical manual of mental disorders (DSM-V) (American Psychiatric Association 2013) delirium is characterized by the disturbance in attention and awareness which develops over a short period of time and tends to fluctuate in severity during the day, often with worsening at night when external stimuli decrease. Besides that, there are disturbances in cognition such as perception disruption which may include misinterpretations, illusions, or hallucinations (American Psychiatric Association 2013). However, there is always clear evidence that all these symptoms are a consequence of another medical condition, intoxication, or withdrawal. Other symptoms associated with delirium are a disturbance in the sleep-wake cycle with excessive nighttime agitation and rapid shifts in emotional states which can be manifested in screaming, calling out or making strange sounds. All these

symptoms can be sometimes difficult to distinguish from acute psychosis since individuals with the brief psychotic disorder (BPD) also usually experience anxiety or overwhelming confusion, and they may have rapid shifts from one intense effect to another. Differential diagnosis between a BPD and psychotic disorder due to another medical condition, delirium, or substance-related disorders can be determined when there is clear evidence from the medical history, physical examination, laboratory or other diagnostic tests that symptoms are the consequence of one of these conditions (American Psychiatric Association, 2013). Table 1. shows the differences in diagnostic criteria for the BPD and delirium based and DSM-V in compare with symptoms our five described patients were presented with.

The findings of 2012 meta-analysis support the hypothesis that cannabis consumption plays a causal role in the development of psychotic disorders in some patients. This also invites new treatment possibilities for people with schizophrenia, where the main target could be endo-cannabinoid receptors (Newall et al. 2012). Areas for the future study also include how cannabis use might interact with psychiatric medications since there are little data investigating how cannabis may acutely affect the efficacy of antipsychotics. In our study, all patients were given the same medication, but the clinical response in each patient was different. Also, during the hospitalization period, especially in the early acute phase with severe aggressive symptoms, patients were treated with high doses of anxiolytics in order to effectively and quickly reduce their unpredictable and hostile behaviour. It is interesting to draw the line across delirium treatment in which patients also promptly response to given anxiolytics, so our patients can be somehow compared to acute confused state such as delirium. If we could gain a better understanding of how cannabis could affect psychiatric medications, we might be able to adjust the medicine prescribed to a specific patient (Johnson et al. 2016). Current evidence supports the fact that high levels of cannabis use can increase the risk for psychotic outcomes in a dose-dependent way. Although a causal link cannot be established, there is sufficient proof to justify harm reduction prevention programs (Henquet et al. 2005). A pilot version of such programme has taken a leap under the slogan "Clear head without weed" within the Centre for integrative psychiatry (CIP) multimodal Early Intervention Services in the form of the Day Hospital for Addictive Disorders in "Sveti Ivan" Psychiatric Hospital in Zagreb, Croatia. The programme consists of eight psychoeducational workshops in the form of a group with between 10-12 patients who experienced FEP triggered by cannabis consumption. It is focused to change problematic cannabis use in those patients, to prevent subsequent episodes and further impairment. It is based on several psychotherapies, and psychoeducational approaches and every single workshop covered one specific area, with hope to help patients to recognize the link between cannabis use and psychosis. It is not irrelevant to mention the effect of the environmental factor as well as the influence of personality traits on the course of the treatment. This can be one of the reasons for therapeutic non-adherence and relapse of the disease.

CONCLUSION

The clinical presentation of FEP in cannabis users can be atypical and highly unpredictable from mild psychotic symptoms to severe substance intoxication delirium. In clinical practice clinicians treating new onset psychosis need to be watchful for cannabis and synthetic cannabinoids induced psychosis. Pharmacotherapeutic interventions include prompt and adequate use of the benzodiazepine, second-generation antipsychotic, and mood-stabilizers. Further research in the pharmacotherapy of cannabis-induced psychosis is required

Acknowledgements:

The study was funded by Psychiatric Hospital "Sveti Ivan", Zagreb, Croatia.

Conflict of interest: None to declare.

Contribution of individual authors:

All authors contributed to the conception of this manuscript, the literature search, the interpretation of the obtained results, participated in drafting and revising the article critically.

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